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Exposure to Outdoor Particulate Matter Air Pollution and Risk of Gastrointestinal Cancers in Adults: A Systematic Review and Meta-Analysis of Epidemiologic Evidence

Natalie Pritchett,[1] Emily C. Spangler,[2] George M. Gray,[3] Alicia A. Livinski,[4] Joshua N. Sampson,[1] Sanford M. Dawsey,[1] and Rena R. Jones[1]

[1]National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA
[2]Global Health Section, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[3]Department of Environmental and Occupational Health, Milken Institute School of Public Health, George Washington University, Washington DC, USA
[4]National Institutes of Health Library, Office of Research Services, National Institutes of Health, Bethesda, Maryland, USA

Background: Outdoor air pollution is a known lung carcinogen, but research investigating the association between particulate matter (PM) and gastrointestinal (GI) cancers is limited.

Objectives: We sought to review the epidemiologic literature on outdoor PM and GI cancers and to put the body of studies into context regarding potential for bias and overall strength of evidence.

Methods: We conducted a systematic review and meta-analysis of epidemiologic studies that evaluated the association of fine PM [PM with an aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$)] and PM_{10} (aerodynamic diameter $\leq$10 μm) with GI cancer incidence or mortality in adults. We searched five databases for original research published from 1980 to 2021 in English and summarized findings for studies employing a quantitative estimate of exposure overall and by specific GI cancer subtypes. We evaluated the risk of bias of individual studies and the overall quality and strength of the evidence according to the Navigation Guide methodology, which is tailored for environmental health research.

Results: Twenty studies met inclusion criteria and included participants from 14 countries; nearly all were of cohort design. All studies identified positive associations between PM exposure and risk of at least one GI cancer, although in 3 studies these relationships were not statistically significant. Three of 5 studies estimated associations with PM_{10} and satisfied inclusion criteria for meta-analysis, but each assessed a different GI cancer and were therefore excluded. In the random-effects meta-analysis of 13 studies, $PM_{2.5}$ exposure was associated with an increased risk of GI cancer overall [risk ratio (RR) = 1.12; 95% CI: 1.01, 1.24]. The most robust associations were observed for liver cancer (RR = 1.31; 95% CI: 1.07, 1.56) and colorectal cancer (RR = 1.35; 95% CI: 1.08, 1.62), for which all studies identified an increased risk. We rated most studies with "probably low" risk of bias and the overall body of evidence as "moderate" quality with "limited" evidence for this association. We based this determination on the generally positive, but inconsistently statistically significant, effect estimates reported across a small number of studies.

Conclusion: We concluded there is some evidence of associations between $PM_{2.5}$ and GI cancers, with the strongest evidence for liver and colorectal cancers. Although there is biologic plausibility for these relationships, studies of any one cancer site were few and there remain only a small number overall. Studies in geographic areas with high GI cancer burden, evaluation of the impact of different PM exposure assessment approaches on observed associations, and investigation of cancer subtypes and specific chemical components of PM are important areas of interest for future research. https://doi.org/10.1289/EHP9620

Introduction

Gastrointestinal (GI) cancers are a major cause of cancer burden and cancer death. Worldwide, there were an estimated 4.8 million new cases of GI cancers and 3.4 million GI cancer deaths in 2018[1]. In addition, four of the five cancer sites with the worst prognosis (esophagus, stomach, pancreas, liver, and lung) are GI cancers.[2]

Particulate matter (PM) is a common aerosol outdoor pollutant arising from both natural and anthropogenic sources that has widespread geographic heterogeneity in both its levels and chemical composition.[3,4,5] Respirable PM is of greatest concern for human health,[5] including particles $\leq$10 μm in aerodynamic diameter (PM_{10}), fine particles [$\leq$2.5 μm ($PM_{2.5}$)], and intermediate-sized particles [2.5–10 μm (coarse PM)].[5,6] There is a large body of epidemiologic evidence demonstrating associations between exposure to PM and other outdoor air pollutants and risk of adverse noncancer health effects, including chronic obstructive pulmonary disease, asthma, and cardiovascular diseases.[7,8] In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution, specifically PM, as a human carcinogen.[9]

The IARC classification of PM as a carcinogen was primarily based on evidence that long-term exposure causes lung cancer; in human populations, this association has been consistently demonstrated in both case–control and cohort studies.[9] However, it is possible that exposure is associated with cancer at sites other than the lung owing to exposure through absorption, metabolism, and distribution of inhaled carcinogens released as primary PM emissions or bound to particles, including polycyclic aromatic hydrocarbons, other volatile organic compounds, and heavy metals.[9,10] Increasingly, evidence has grown for associations with other organ sites, such as the breast, as recently reviewed by Gabet et al.[11] Hypothesized general mechanisms of carcinogenicity for PM-related cancers include DNA damage due to oxidative stress and PM-induced inflammation that promotes tumor growth.[12] Mechanisms more specific to GI cancers include alterations in the function of the gut microbiota[13] and the delivery of small particles absorbed in the lungs through the bloodstream to the gut.[14] PM that reaches the bronchioles and alveolar spaces may also be propelled into the GI tract via mucociliary clearance,[15] a process that has been demonstrated in human studies of nonsmokers.[16]

Rationale

Despite biologic plausibility, there has been little research to date on the association between outdoor PM, a common pollutant of interest, and GI cancers. A small number of reviews have found

Address correspondence to Rena R. Jones, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr., 6E606, Rockville, MD 20892 USA. Telephone: (240) 276-7292. Email: rena.jones@nih.gov

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evidence of associations between PM and esophageal, stomach, colorectal, liver, and other cancers.[10,17,18,19,20] A systematic review of cohort studies evaluating associations of PM and cancer mortality showed a positive, statistically significant $PM_{2.5}$ association with deaths from liver and colorectal cancers.[17] Notably, that review included very few articles from countries and geographic areas with exceptionally high burdens of PM air pollution or upper GI cancers, such as Africa, where rates of esophageal cancers are among the highest globally[1] and where distinct geographic regions of elevated esophageal cancer incidence are not well understood.[21] A review focused on biomass air pollution and upper GI cancers in sub-Saharan Africa found positive associations between exposure to biomass smoke and both esophageal and gastric cancers.[18] A meta-analysis of case–control studies of household air pollution and cancers other than lung cancer found positive associations with a number of cancers, including an elevated but nonsignificant risk for esophageal cancer.[19] In the present systematic review and meta-analysis, we reviewed the literature regarding primary cancers of the esophagus, stomach, colorectum, anus, liver, biliary tract, and pancreas for associations with PM. We aimed to collect and assess the available epidemiologic research on the relationship between PM air pollution and GI cancers, characterize the quality of the existing evidence, identify research gaps, and provide recommendations for future research.

Study Question

Our primary research question was "Is exposure to PM in humans associated with the incidence or mortality of GI cancer?" Our population of interest was human adults living in any geographic location. Our definition of "air pollution" exposure was any outdoor source of any inhaled PM, excluding active and passive smoking. Our comparators were individuals exposed to lower levels of PM and those that are more highly exposed. The outcome of interest in our review was clinically confirmed diagnosis of GI cancer or death due to GI cancer.

Methods

Protocol

This systematic review follows the structure outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[22,23,24] (Table S1). A protocol was registered with PROSPERO prior to beginning the review (ID 139597). Our methods were tailored to follow the steps outlined in the Navigation Guide Systematic Review Methodology, which was developed to synthesize and evaluate environmental evidence.[25] This approach specifically seeks to reduce bias and maximize transparency in the synthesis of environmental research and has two unique departures from existing methodologies that have been established for evidence-based medicine assessments in the clinical sciences: *a*) observational studies are assigned a "moderate" quality rating by default, and *b*) a standard nomenclature is used for describing the weight of evidence across diverse types of studies.

Search Strategy and Information Sources

Five citation and abstracts databases: PubMed (U.S. National Library of Medicine), EMBASE (Elsevier), Cochrane Library: Database of Systematic Reviews (Wiley & Sons), Scopus (Elsevier), and Web of Science: Core Collection, Russian Citation Index, SciELO: (Clarivate Analytics) were searched by a biomedical librarian (A.A.L.) in July 2019 and were also updated in March and September of 2021. Searches were limited to original research articles published in English between 1980 and September 2021 and with human subjects. Keywords and controlled vocabulary (e.g., MeSH, Emtree) were used to describe each outcome (e.g., "gastrointestinal cancer") and environmental exposure (e.g., "particulate matter," "outdoor air pollution") of interest. The final search strategy for PubMed is provided in Table 1. (Table S2 lists all the database search strategies used.) EndNote X9 (Clarivate Analytics) was used to collect, manage, and identify duplicate citations. Additional articles were identified by searching the reference lists of all included studies as well as review articles identified in the screening process.

Study Eligibility Criteria and Study Selection

Covidence (Veritas Health Innovation Ltd.) was used for study selection (i.e., screening).[26] Prior to conducting the full review, two authors (N.P., E.C.S.) tested the utility of their screening criteria during a pilot test of 330 articles. The pilot test informed the use of less restrictive criteria in the title and abstract screening than in the full-text screening and helped clarify interrater discrepancies. The final eligibility criteria for title and abstract screening were the presence of at least one term regarding the exposure of interest: "particulate matter," "air pollution," and at least one general term for the outcome of interest: "cancer." The article also needed to be a peer-reviewed publication (e.g., no conference abstracts), published in English, and conducted in humans.

First, two authors (N.P., E.C.S.) independently screened the titles and abstracts using the eligibility criteria above. Next, the full text of each screened article was assessed independently by two authors (N.P., E.C.S.) using a stricter set of criteria. For the full-text screening, the following eligibility criteria were used: an association between PM and at least one GI cancer end point (incidence or mortality) in adults ($\geq$18 years of age) was evaluated using a cohort or case–control study design; we also considered time-series analyses with individual-level data. Articles were excluded if they did not report, or if we could not obtain, effect estimates for PM_{10} or $PM_{2.5}$ with concurrent standard errors or confidence intervals (CIs). Disagreements during both title and abstract and full-text screening were resolved by discussion or in consultation with a third author. Final determinations about inclusion in the systematic review were made when all issues regarding eligibility criteria had been resolved between both reviewers. Articles excluded during the full-text screening with the reasons for exclusion are listed in Excel Table S1.

Data Extraction

Two authors (N.P., E.C.S.) independently extracted data related to study characteristics from each included article using Covidence. A third author was consulted to resolve discrepancies between these two authors. The descriptive characteristics extracted from each article were: first author, year published, location of study first author, study design, study population, outcome assessment method, exposure(s) assessed, exposure assessment method, exposure window, study time period, study participant location, and the reported measure of association.

We also extracted all relevant estimates of association relating PM exposure (for any individual or group of individuals) with GI cancer. We extracted fully adjusted regression estimates and 95% CIs for use in meta-analysis.

Study Quality

Risk of bias assessment for each included study. Two authors (N.P., E.C.S.) evaluated the risk of bias for each of our included articles using a modified set of criteria we developed based on

Table 1. Final PubMed search strategy for the systematic review and meta-analysis of PM exposure and GI cancer incidence and mortality.

Concept	Search terms used
Gastrointestinal cancer	("Esophageal cancer"[tiab] OR "Esophageal cancers"[tiab] OR "oesophageal cancer"[tiab] OR "oesophageal cancers"[tiab] OR "Gastric cancer"[tiab] OR "Gastric cancers"[tiab] OR "esophageal adenocarcinoma"[tiab] OR "esophageal adenocarcinomas"[tiab] OR "oesophageal adenocarcinoma"[tiab] OR "oesophageal adenocarcinomas"[tiab] OR "Upper aerodigestive tract cancer"[tiab] OR "Upper aerodigestive tract cancers"[tiab] OR "Stomach cancer"[tiab] OR "Stomach cancers"[tiab] OR "esophageal squamous cell carcinoma"[tiab] OR "esophageal squamous cell carcinomas"[tiab] OR "oesophageal squamous cell carcinoma"[tiab] OR "oesophageal squamous cell carcinomas"[tiab] OR "Upper gastrointestinal cancer"[tiab] OR "Upper gastrointestinal cancers"[tiab] OR "Esophageal neoplasm"[tiab] OR "Esophageal neoplasms"[tiab] OR "oesophageal neoplasm"[tiab] OR "oesophageal neoplasms"[tiab] OR "Gastric neoplasm"[tiab] OR "Gastric neoplasms"[tiab] OR "esophageal adenocarcinoma"[tiab] OR "esophageal adenocarcinomas"[tiab] OR "oesophageal adenocarcinoma"[tiab] OR "oesophageal adenocarcinomas"[tiab] OR "Upper aerodigestive tract neoplasms"[tiab] OR "Stomach neoplasm"[tiab] OR "Stomach neoplasms"[tiab] OR "esophageal squamous cell carcinoma"[tiab] OR "esophageal squamous cell carcinomas"[tiab] OR "oesophageal squamous cell carcinoma"[tiab] OR "oesophageal squamous cell carcinomas"[tiab] OR "Upper gastrointestinal neoplasm"[tiab] OR "Upper gastrointestinal neoplasms"[tiab] OR "alimentary carcinoma"[tiab] OR "gastrointestinal cancer"[tiab] OR "gastrointestinal cancers"[tiab] OR "gastrointestinal neoplasm"[tiab] OR "gastrointestinal neoplasms"[tiab] OR "Gastrointestinal Tract Cancer"[tiab] OR "Gastrointestinal Tract Cancers"[tiab] OR "Gastrointestinal Neoplasms"[tiab] OR "liver cancer"[tiab] OR "liver cancers"[tiab] OR "hepatic neoplasms"[tiab] OR "hepatic neoplasm"[tiab] OR "liver neoplasm"[tiab] OR "liver neoplasms"[tiab] OR "hepatic cancer"[tiab] OR "hepatic cancers"[tiab] OR "hepatic neoplasm"[tiab] OR "hepatic neoplasms"[tiab] OR "hepatocellular cancer"[tiab] OR "hepatocellular cancers"[tiab] OR "hepatocellular neoplasm"[tiab] OR "hepatocellular neoplasms"[tiab] OR cholangiocarcinoma OR cholangiocarcinomas OR "cholangiocellular carcinoma"[tiab] OR "cholangiocellular carcinomas"[tiab] OR "extrahepatic cholangiocarcinoma"[tiab] OR "extrahepatic cholangiocarcinomas"[tiab] OR "intrahepatic cholangiocarcinoma"[tiab] OR "intrahepatic cholangiocarcinomas"[tiab] OR "pancreatic cancer"[tiab] OR "pancreatic cancers"[tiab] OR "pancreatic neoplasm"[tiab] OR "pancreatic neoplasms"[tiab] OR "pancreas cancer"[tiab] OR "pancreas cancers"[tiab] OR "pancreas neoplasm"[tiab] OR "pancreas neoplasms"[tiab] OR "biliary cancer"[tiab] OR "biliary cancers"[tiab] OR "biliary neoplasm"[tiab] OR "biliary neoplasms"[tiab] OR "biliary carcinoma"[tiab] OR "biliary carcinomas" [tiab] OR "bile duct cancer" [tiab] OR "bile duct cancers"[tiab] OR "bile duct neoplasm"[tiab] OR "bile duct neoplasms"[tiab] OR "biliary tract neoplasm"[tiab] OR "biliary tract neoplasms"[tiab] OR "biliary tract cancer"[tiab] OR "biliary tract cancers"[tiab] OR "bile duct carcinoma"[tiab] OR "bile duct carcinomas"[tiab] OR "colon cancer"[tiab] OR "colon cancers"[tiab] OR "colon neoplasm"[tiab] OR "colon neoplasms"[tiab] OR "colonic neoplasm"[tiab] OR "colonic neoplasms"[tiab] OR "colonic cancer"[tiab] OR "colonic cancers"[tiab] OR "rectal cancer"[tiab] OR "rectal cancers"[tiab] OR "rectal neoplasm"[tiab] OR "rectal neoplasms"[tiab] OR "rectum cancers"[tiab] OR "rectum cancer"[tiab] OR "colorectal cancer"[tiab] OR "colorectal cancers"[tiab] OR "colorectal neoplasm"[tiab] OR "colorectal neoplasms"[tiab] OR carcinoid[tiab] OR carcinoids[tiab] OR "duodenal cancer"[tiab] OR "duodenal cancers"[tiab] OR "duodenal neoplasm" [tiab] OR "duodenum cancer"[tiab] OR "duodenum cancers"[tiab] OR "duodenal neoplasms"[tiab] OR "small bowel cancer"[tiab] OR "small bowel cancers"[tiab] OR "small bowel neoplasm"[tiab] OR "small bowel neoplasms"[tiab] OR "gallbladder cancer"[tiab] OR "gallbladder cancers"[tiab] OR "gallbladder neoplasm"[tiab] OR "gallbladder neoplasms" [tiab] OR "gall bladder cancer"[tiab] OR "gall bladder cancers"[tiab] OR "gall bladder neoplasm"[tiab] OR "gall bladder neoplasms"[tiab] OR "anal cancer"[tiab] OR "anal cancers"[tiab] OR "anal neoplasm"[tiab] OR "anal neoplasms"[tiab] OR "anus cancer"[tiab] OR "anus cancers"[tiab] OR "anus neoplasm"[tiab] OR "anus neoplasms"[tiab] OR "Liver Neoplasms"[Mesh] OR "Cholangiocarcinoma"[Mesh] OR "Pancreatic Neoplasms"[Mesh] OR "Biliary Tract Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh] OR "Duodenal Neoplasms"[Mesh] OR "Gallbladder Neoplasms"[Mesh] OR "Anus Neoplasms"[Mesh] OR "Carcinoid Tumor"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR "Adenocarcinoma Of Esophagus" [Supplementary Concept] OR "Esophageal Squamous Cell Carcinoma"[Mesh] OR "Gastrointestinal Neoplasms"[Mesh])
	AND
Particulate matter/air pollution	("air pollution"[tiab] OR "Particulate Air Pollutants"[tiab] OR "Particulate Air Pollutant"[tiab] OR "particulate matter"[tiab] OR "particulate matters"[tiab] OR "particular matter"[tiab] OR "particular matters"[tiab] OR "air pollutant"[tiab] OR "air pollutants"[tiab] OR "particle pollutant"[tiab] OR "particle pollutants"[tiab] OR "particle pollution"[tiab] OR "fine PM"[tiab] OR "pm2 5"[tiab] OR pm10[tiab] OR "Air Pollution"[Mesh] OR "Particulate Matter"[Mesh] OR "Air Pollutants"[Mesh])
Limits applied	Language: English Publication date: 1 January 1980–31 December 2019; 1 January 2019–31 December 2020; 1 January 2020–31 December 2021

Note: The limits for language (English) and publication year (1980–2021) were applied to the main search using the filters available in PubMed. The keywords were searched in the title and abstract fields in PubMed (i.e., "[tiab]") and the controlled vocabulary terms are indicated with "[Mesh]." Phrases were enclosed in quotation marks to force the searching of the exact terms in order presented. No other limits were applied to the searches. GI, gastrointestinal; PM, particulate matter.

the Cochrane Collaboration's risk of bias tool and the Agency for Health care Research and Quality's (AHRQ) domains.[27,28] We modified the AHRQ domains to make them specific for environmental health studies and evaluated the most common domains in epidemiologic studies: study group, outcome assessment, exposure assessment, covariates, statistical analysis, and conflict of interest. Each domain was rated based on qualities used in the U.S. Environmental Protection Agency's assessments of the scientific data on air pollutants for the National Ambient Air Quality Standards review process to evaluate studies, which are described in detail below and the "low" risk of bias is summarized as an example in Table 2.[29] The possible ratings for each article for each domain were "low," "probably low," "probably high," or "high" risk of bias. We assumed an initial rating of "moderate" quality for all studies based on the limitations of observational data in assessing associations between exposure and health outcomes in environmental health research, per Navigation Guide methodology.

Study group representation was rated as "low" risk of bias if the study population was large and covered a wide geographic area (defined as multiple states or countries vs. a single city, state, or comparable geo-administrative unit). To be rated as "low" risk of bias for detection of health outcome, the study had to use the International Classification of Diseases to classify clinically

Table 2. Risk of bias domains under the low risk designation for individual studies included in the systematic review of PM exposure and GI cancers.

Risk of bias domain	Low risk of bias designation
Study design	Retrospective or prospective cohort analysis of individuals.
Study group representation	Study population is large and covers a wide geographic area.
Outcome assessment	Any missing outcome data is not likely to introduce bias.
Exposure assessment	Risk of exposure misclassification is minimized through refined methods.
Confounding	Important potential confounders such as socioeconomic status, smoking status, and occupational exposure were appropriately accounted for in the analysis.
Statistical analysis	Modifying effects assessed by stratified analyses, sensitivity analysis for change of residence, model check for non-linear exposure, adjustment for multiple comparisons.
Conflict of interest	Study free of support from individual or entity having financial interest in outcome of study.

Note: GI, gastrointestinal; PM, particulate matter.

confirmed diagnosis of GI cancer by subtype. To be rated as "low" risk of bias for exposure assessment, the study had to use an approach that estimated PM exposure along with at least one other co-occurring pollutant using measurement data from air quality surveillance networks or was estimated via land-use regression (LUR) or other types of prediction models. The exposures must have been quantitatively estimated at the individual level (i.e., residence or personal exposure) before or during the study period. For statistical analysis, studies had to use multipollutant models and control for other important confounders at the individual level [e.g., age, sex, socioeconomic status (SES), smoking status, occupational exposure]. Studies of multiple cancer end points had to adjust for multiple comparisons, examine the impact of an exposure time lag, conduct sensitivity analyses for change of residence, and assess potential effect measure modification by stratified analyses. In addition, evaluation of nonlinear relationships was a strength, given the potential for associations only at the high end of exposure; studies that did not include nonlinear evaluations were downgraded. To be rated as "low" risk of bias for conflict of interest, the study had to acknowledge that there were no author conflicts. Based on the summary quality rating for each study, we also determined an overall quality rating across all studies.

Strength of evidence across studies. To assess the strength of the evidence across all studies included in the present review, two authors (N.P., E.C.S.) used categories based on the classification scheme in the IARC's monographs (which evaluate epidemiologic, as well as animal and mechanistic, findings) to assign an overall strength rating of "sufficient evidence of carcinogenicity," "limited evidence of carcinogenicity," "inadequate evidence of carcinogenicity," or "inadequate evidence regarding carcinogenicity."[30] The overall strength of the body of epidemiologic evidence we reviewed was based on three main considerations: *a*) quality of the body of evidence based on the confidence in direction of effect, *b*) overall rating from the risk of bias assessment, and *c*) likelihood that a new study would change the summary conclusion about associations with cancer risk.

Statistical analyses. Two authors (N.P., E.C.S.) extracted from each study the fully adjusted hazard ratios (HRs), risk ratios (RRs), incidence rate ratios (IRRs), odds ratios (ORs) and the corresponding estimates of the 95% CIs, and the increment increase in exposure. Noncontinuous estimates of association were not standardized and are shown in their original format. We standardized all continuous effect estimates by computing adjusted risk estimates and their 95% CI per 10-$\mu g/m^3$ increase in $PM_{2.5}$ or PM_{10} concentrations by applying the following formula:

$$Effect\ Estimate_{Standardized} = e^{\left(\frac{\ln(Effect\ Estimate_{Original})}{Increment_{Original}} \times Increment_{Standardized}\right)}.$$

Random-effects (RE) meta-analyses were performed using the DerSimonian-Laird method [31] using Stata (version 15; StataCorp). The RE analyses were conducted using estimates from fully adjusted models to obtain a single summary estimate across studies that had sufficient quality ("low" or "probably low" risk of bias) and the ability to standardize outcome estimates in a meaningfully comparative way. We excluded studies from the meta-analysis that were rated "high" or "probably high" risk of bias or did not have more than two studies of similar design to provide a comparison. We considered the IRR, HR, RR, and OR effectively interchangeable for these relatively rare GI cancers (i.e., IRR $\approx$ HR $\approx$ RR $\approx$ OR). We also combined incidence and mortality for these analyses, given that mortality for most of these cancers can be considered a reasonable indicator of incidence and the small numbers of studies evaluating each of these outcomes. Statistical heterogeneity across study estimates was evaluated using Cochran's Q statistic (with $p \leq 0.05$ as the threshold for statistical significance) and I^2.[27] For cancer outcomes that were not amenable to a meta-analysis (i.e., due to insufficient number of studies or heterogeneity in study designs), the estimates of association were standardized and considered in the final rating of the overall body of evidence. We assessed possible publication bias using visual inspection of funnel plots and Egger's regression-based test.[32]

We quantitatively evaluated the potential impact that the addition of one or more new studies might have on changing the interpretation of our overall evaluation of the literature. Specifically, we determined what magnitude of association would need to be reported by a hypothetical new study to reverse the direction of association. In making this calculation, we first assumed that the 95% CI for the new hypothetical study would be as narrow as the smallest 95% CI included in our analysis. We then added hypothetical new studies (with CI determined as described) until the direction of the summary estimate changed. If the summary estimate was not statistically significant in the meta-analysis, we further added more hypothetical new studies of similar magnitude and CI until the summary estimates became significant.

Results

Literature Search and Study Selection

Initial searches yielded 2,423 publications of which 936 were duplicates and 1,487 citations were screened. After title and abstract screening, 1,367 sources were excluded, with 120 studies proceeding to full-text screening. Twenty studies were selected at the end of full-text screening and included in the systematic review (Figure 1). Of those excluded, 68 did not quantitatively assess exposure to $PM_{2.5}$ or PM_{10}; were not a cohort or case–control study ($n = 11$); the outcome was not GI cancer ($n = 16$), conference abstract ($n = 3$), or not published in English ($n = 2$) (Table S3).

The earliest of the 20 studies included was published in 2005 (Table 3).[13,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51] Baseline data collection began in 1982 to 2016, and follow-up periods ranged from 5 to 27 y. All included studies were retrospective

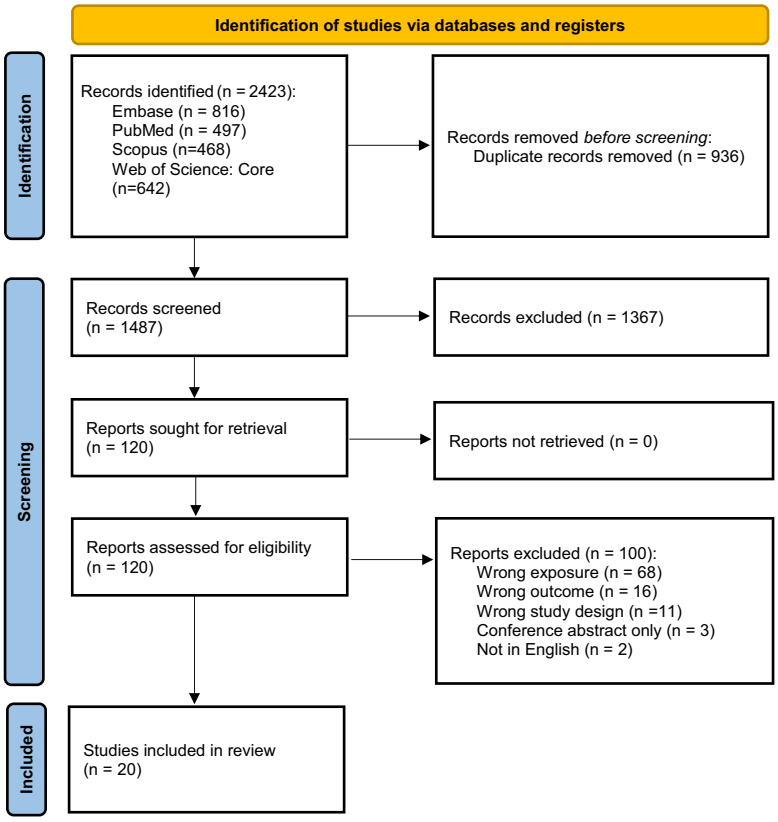

Figure 1. PRISMA flow diagram showing the literature search and screening process for studies relevant to PM exposure and GI cancer outcomes. Note: GI, gastrointestinal; PM, particulate matter; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

or prospective cohort analyses except for one nested case–control study[48] and one time-series analysis with individual-level medical records,[47] and exposures were directly linked to individuals or geographic area (e.g., county, ZIP code). All included studies were conducted in the northern hemisphere: Asia,[13,40,44,46,47,48,51] Europe,[33,36,39,41,45,50] the United States, or Canada.[34,35,37,38,42,43,49]

Risk of Bias within Studies and Strength of Evidence

Most studies were rated as "low" or "probably low" risk of bias in domains other than the statistical analysis (Figure 2). Most studies had large sample sizes (>50,000 participants) and were rated as having sufficient population representation, but some were focused on a circumscribed geographic area.[13,33,36,37,38,40,42,47,48,49,51]

All studies presented confirmed cancer outcomes based on linkage to cancer or death registries, including ($n = 10$) of incident disease and ($n = 10$) of determined mortality due to a GI cancer. Some studies ($n = 9$) had information on cancer subtype. Most studies (15 of 20) could link cancer status to individual study participants.

Exposure assessments were based on a combination of data collected from air quality monitoring stations and satellite-based networks. Two studies relied on directly collected measurements only; one used PM_{10} emissions data collected at a point source,[33] and another effort conducted dedicated 2-wk measurement campaigns.[41] Modeling approaches to estimate exposure at participant locations included kriging,[52] LUR,[53] inverse distance weighting,[54] integrated empirical geographic regression models,[55] Bayesian maximum entropy interpolation,[56] or combinations of these approaches. All but two studies included some estimate of $PM_{2.5}$ exposure (i.e., rather than PM_{10}),[33,36] and all but two estimated risk in relation to a continuous exposure metric.[33,40] Many studies relied on a single year of data to reflect exposure over a longer time period,[33,36,38,39,43,50] and others estimated exposure during the full study period.[35,46,49] No studies estimated exposure for a period prior to recruitment or study start. One study evaluating liver cancer survival estimated exposures post-diagnosis.[37]

Seven of the studies that were rated as "probably low" or "probably high" risk of bias in the exposure assessment domain used area-level data (e.g., within a geo-administrative boundary area, such as a county or across a grid cell) to estimate exposures. Studies were also downgraded if exposure assessment covered a limited time period (≤ 1 y) or did not take place until the end or after the conclusion of cohort follow-up ($n = 7$). No studies estimated exposure during a period prior to study enrollment, but some studies back-extrapolated estimates when exposure data was not available for the full study period.[34,35,49] Eleven studies based exposure estimates on the location of the participant residence at the time of study enrollment. Only 2 studies assessed PM components, and they found statistically significant associations between sulfur PM species and gastric cancer incidence,[45] as well as liver cancer and copper, iron, zinc, sulfur, nickel, vanadium, and silicon components.[50]

Most studies controlled for confounding using methods that would lead to a "low" or "probably low risk" of bias ($n = 15$). The most common features missing from model adjustments were variables such as SES, smoking status, physical activity, and occupational PM exposure. A few studies did not have individual risk factor data ($n = 4$). About half of studies controlled for co-pollutants ($n = 11$).

Statistical analyses were rated as "probably high risk" of bias for 9 of the 20 studies because they did not assess effect modification using stratified analyses across subgroups (e.g., by age, race/ethnicity). Few studies examined the impact of an exposure time

Table 3. Articles included the systematic review and meta-analysis of PM exposure and GI cancers.

No.	Article author	Year published	Location of study	Study design	Study population	Outcome assessment method	Exposures assessed	Exposure assessment method	Exposure window/time period for PM exposures
1	Ancona et al.[33]	2015	Italy	Retrospective cohort analysis of mortality	85,559 individuals in the Rome Longitudinal Study	Admissions data from regional Hospital Information System and death data from regional Registry of Causes of Death	PM_{10}, H_2S, NO_2, SO_X	PM_{10} estimated at each participant address using air dispersion models from an incinerator point source	Hourly PM_{10} concentrations in 2005
2	Bogumil et al.[49]	2021	USA	Prospective analysis of incident pancreatic cancer cases	100,527 men and women in California from the Multiethnic Cohort	California Cancer Registry	$PM_{2.5}$, PM_{10}, NO_2, and NO_x	Kriging interpolation used to estimate each participant's exposure levels at residence; measured concentrations from the U.S. EPA routine air monitoring data; $PM_{2.5}$ concentrations for the years prior to 2000 estimated using a spatiotemporal model	Time-weighted monthly averages of PM_{10} and $PM_{2.5}$, 1993–2013
3	Chu et al.[46]	2020	China	Prospective cohort analysis of colorectal cancer incidence	154,897 individuals in the PLCO Cancer Screening Trial	Diagnosis of colorectal cancer histologically confirmed via medical record reviews, the National Death Index, and self-reported annual questionnaires	$PM_{2.5}$	Mean $PM_{2.5}$ concentrations at 10 study centers derived from U.S. EPA monitoring network	Daily 24-h average $PM_{2.5}$ concentrations 1999–2011 were used to estimate a long-term average exposure from the date of trial entry (January 1999 or beyond) to the date of cancer diagnosis or trial exit
4	Coleman et al.[35]	2020	USA	Prospective cohort analysis of cancer mortality	635,539 individuals in the National Health Interview Study	Mortality data from National Death Index categorized using ICD-10 codes	$PM_{2.5}$	Population-weighted modeled $PM_{2.5}$ exposure at residential census tract; backcasted estimates for 1988–1998	Long-term average $PM_{2.5}$, 1999–2015 and 1988–2015
5	Coleman et al.[34]	2020	USA	Retrospective cohort analysis of cancer incidence	>8.5 million cases of cancer incidence from U.S. registries	Average annual county-level incidence rates from SEER	$PM_{2.5}$	County-level $PM_{2.5}$ concentrations estimated using integrated empirical geographic regression models; backcasted estimates for 1988–1998	Long-term average $PM_{2.5}$, 1988–2015
6	Datzmann et al.[36]	2018	Germany	Semi-individual cohort study of colorectal cancer mortality	1,918,449 members of a large statutory health insurance in Saxony (AOK PLUS), which covers almost half of the local general population	IDC-10 code case definition taken from routine health care inpatient and outpatient data	PM_{10} and NO_2	PM_{10} and NO_2 concentrations estimated from maps at the 100-m^2 area generated using LUR models based on EuroAirnet monitoring sites and linked to participant postal code	Annual PM_{10} concentrations in 2007
7	Deng et al.[37]	2017	USA	Retrospective cohort analysis of liver cancer mortality	22,221 California Cancer Registry patients with hepatocellular carcinoma	California Cancer Registry	$PM_{2.5}$	$PM_{2.5}$ concentrations from the U. S. EPA Air Quality System database monitors near residential address from date of diagnosis to date of death, loss to follow-up, or end of study	Monthly average $PM_{2.5}$ concentrations, 2000–2009

Table 3. (*Continued.*)

No.	Article author	Year published	Location of study	Study design	Study population	Outcome assessment method	Exposures assessed	Exposure assessment method	Exposure window/time period for PM exposures
8	Ethan et al.[47]	2020	China	Retrospective analysis of cancer mortality	Six districts (Beilin, Yanta, Weiyang, Lianhu, Gaoling, and Huyi) within Xi'an, the capital of Shaanxi province, which has a population of ~8.7 million people (2010 census)	Daily cancer mortality data and population data were obtained from the Centers for Disease Control and Prevention, Shaanxi (Xi'an)	$PM_{2.5}$, PM_{10}, O_3, SO_2, NO_2	Compiled from city-wide average data available from Xi'an Environmental Monitoring Stations (13 stations)	Daily $PM_{2.5}$, PM_{10} records for 1,091 d in 2014
9	Guo et al.[51]	2020	Hong Kong	Prospective cohort analysis of GI cancer mortality	385,650 members of a standard medical examination program	Linkage to national death registry database	$PM_{2.5}$	Satellite-based spatiotemporal model estimated ambient $PM_{2.5}$ concentrations using aerosol optical depth data at a resolution of 1 km^2 assigned to participant residential addresses	Annual average $PM_{2.5}$ concentrations, 2006–2014
10	Jerrett et al.[38]	2005	USA	Prospective cohort analysis of digestive cancer mortality	22,905 participants in the American Cancer Society Cancer Prevention Study II	Categorized by ICD 9- and -10 codes based on vital status obtained through interviews, death certificates, and National Death Index	$PM_{2.5}$ and O_3	Data from fixed-site monitors assigned based on ZIP code	Annual average $PM_{2.5}$ in 2000
11	Ma et al.[48]	2020	Taiwan	Nested case–control study of colorectal cancer incidence among a diabetic population	1,164,962 patients newly diagnosed with diabetes	Taiwanese National Health Insurance Research Database with ICD-9 codes	$PM_{2.5}$, PM_{10}, SO_2, NO, NO_2, CO, and O_3	Measured at 76 monitoring stations from the Taiwan Environmental Protection Administration. Kriging was used to approximate the $PM_{2.5}$ level at each participant's residential address using data from the nearest monitoring station	Annual average $PM_{2.5}$ concentrations, 1999–2013
12	Nagel et al.[39]	2018	Germany	Prospective cohort analysis of esophageal and gastric cancer incidence	305,551 participants from 11 cohorts in the large European multicenter ESCAPE study	Linkage to national and local cancer registries hospital discharge and mortality data used when registry was not available	$PM_{2.5}$, PM_{10}, PM coarse, $PM_{2.5}$ absorbance, NO_2, NO_x	Exposures at baseline home address estimated using area-specific LUR models	$PM_{2.5}$, PM_{10}, PM coarse, 2008
13	Pan et al.[40]	2016	Taiwan	Prospective cohort analysis of liver cancer incidence	23,820 participants from seven townships on the main Taiwan island and Penghu Islands	Linkage to national cancer registry and death certification systems	$PM_{2.5}$	Hourly ambient $PM_{2.5}$ concentrations measured at fixed-site monitors with modified ordinary kriging applied to approximate the long-term residential exposure to $PM_{2.5}$ for each participant	Long-term average $PM_{2.5}$, 2006–2009
14	Pedersen et al.[41]	2017	Denmark	Prospective cohort analysis of liver cancer incidence	174,770 participants from 4 cohorts in the ESCAPE study	Linkage to population-based cancer registries	$PM_{2.5}$, PM_{10}, PM coarse, PM absorbance, NO_2, NO_x, traffic density	Exposures at baseline home address estimated using area-specific LUR models	Average PM exposures in ~1995 estimated from monitor measurements collected in 2008–2011

Table 3. (*Continued.*)

No.	Article author	Year published	Location of study	Study design	Study population	Outcome assessment method	Exposures assessed	Exposure assessment method	Exposure window/time period for PM exposures
15	So et al.[50]	2021	Denmark	Prospective cohort analysis of liver cancer incidence	367,404 participants from six pooled cohorts	Cancer diagnosis data from national and state cancer registries	NO_2, $PM_{2.5}$, BC, and O_3	Europe-wide hybrid LUR models at a fine spatial scale (100×100 m grids) to estimate annual mean exposure to air pollutants at the participants' residential addresses at baseline	Annual average $PM_{2.5}$ in 2010
16	Turner et al.[42]	2017	Canada	Prospective cohort analysis of cancer mortality	623,048 participants of the American Cancer Society Cancer Prevention Study II	Categorized by ICD 9- and -10 codes based on vital status obtained through interviews, death certificates, and National Death Index	$PM_{2.5}$, NO_2, O_3	LUR and BME interpolation model at 1-km^2 area based on data collected monthly from 1999–2008 linked to participant residence	Long-term average $PM_{2.5}$, 1999–2004
17	VoPham et al.[43]	2018	USA	Retrospective cohort analysis of liver cancer incidence	56,245 newly diagnosed cases from 16 population-based cancer registries	SEER cancer registry	$PM_{2.5}$	U.S. EPA Air Quality System data with an IDW model at the county level and linked to county at confirmed cancer diagnosis	Annual average $PM_{2.5}$ in 2000
18	Wang et al.[44]	2018	China	Spatial age-period cohort analysis of pancreatic cancer mortality	103 area-level points with a population coverage of over half a million people	China national mortality surveillance system	$PM_{2.5}$	Exposure data from the Global Burden of Disease Study 2015 was used to estimate annual concentrations of $PM_{2.5}$ at a $0.1^\circ \times 0.1^\circ$ spatial resolution	Annual average $PM_{2.5}$ concentrations in 1990, 1995, 2000, 2005, and 2010
19	Weinmayr et al.[45]	2018	Germany	Prospective cohort analysis of esophageal and gastric cancer incidence	227,044 study participants from 10 cohorts in the ESCAPE study	Linkage to national or local cancer registries with ICD-9 and -10 code-based case definitions	$PM_{2.5}$ components copper, iron, zinc, sulfur, nickel, vanadium, silicon, and potassium	Exposures at baseline home address estimated using area-specific LUR models; PM filters were analyzed for elemental composition using X-ray fluorescence	Annual averages estimated for varying baseline periods (most mid-1990s) from exposure measurement campaigns conducted in 2008–2011
20	Wong et al.[13]	2016	Hong Kong	Prospective cohort analysis of GI cancer mortality	66,820 enrollees in the Elderly Health Service (≥65 years of age)	Linkage to Hong Kong death registry	$PM_{2.5}$	$PM_{2.5}$ concentrations based on combined monitoring stations and satellite-based data estimated at 1 km^2	Annual average $PM_{2.5}$ for recruitment year (between 1998 and 2001)

Note: BC, black carbon; BME, Bayesian maximum entropy; CO, carbon monoxide; ESCAPE, European Study of Cohorts for Air Pollution Effects; GI, gastrointestinal; H_2S, hydrogen sulfide; ICD, International Classification of Diseases; IDW, inverse distance weighting; LUR, land-use regression model; MEC, Multiethnic Cohort; NCI, National Cancer Institute; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PM, particulate matter; PM coarse, PM 2.5–10 μm in aerodynamic diameter; $PM_{2.5}$, PM ≤2.5 μm in aerodynamic diameter; PM_{10}, PM ≤10 μm in aerodynamic diameter; SEER, Surveillance, Epidemiology, and End Results Program; SO_2, sulfur dioxide; SO_X, sulfur oxides.

Figure 2. Risk of bias ratings for 20 included human studies relevant to PM exposure and GI cancer incidence and mortality. Ancona et al.,[33] Datzmann et al.,[36] Ethan et al.,[47] Jerrett et al.,[38] Pan et al.,[40] Wang et al.,[44] and Weinmayr et al.[45] were excluded from meta-analysis because of their overall rating of "probably high risk of bias" or heterogeneity in study design leading to limitations in comparability with other studies. Note: GI, gastrointestinal; PM, particulate matter.

lag ($n=6$), a common strategy to account for disease latency in cancer analyses, or adjusted p-value estimates to account for multiple comparisons ($n=4$). More than half of the included studies evaluated nonlinearity in models using splines, trends across quartile categories, or quadratic terms ($n=13$). Additional detail on individual study characteristics and risk of bias designation/rationale is presented in Table S2. The overall study rating across the 20 articles was determined as "probably low risk of bias", therefore we rated the overall quality of the current body of evidence as "moderate" (Figure 2).

Statistical Analysis Results from Individual Studies

The HR was the most commonly reported measure of association ($n=12$); we present fully adjusted model estimates from the studies (Table 4). Four studies reported a RR, three reported IRRs, and one reported an OR. Most used a 10-$\mu g/m^3$ increment as a unit change for risk estimates, but some studies reported associations for study-specific quantile increments ($n=2$). With the exception of liver cancer, the majority of studies for any one cancer site evaluated mortality as the end point. The one study of incident colorectal cancer included in our review was a nested case–control study within a population of diabetic individuals that we excluded from our meta-analysis because of this noncomparability in design to other studies.

The majority of studies identified at least one statistically significant positive association between PM exposure and risk of at least one GI cancer end point for incidence or mortality ($n=16$). Overall, associations were observed for GI tract, upper GI tract, and GI accessory organs, as well as for specific cancer sites, including stomach, colorectal, rectal, liver, and pancreas. There were no significant associations reported with esophageal cancer; however, only 4 of our included studies evaluated this site.[34,35,39,42] Four of the 20 studies reported no statistically significant association [2 on liver cancer risk,[41,50] 1 on gastric (cardia and non-cardia) and upper aerodigestive tract (adeno and squamous cell) risk,[39] and 1 on digestive cancer mortality overall[38]].

The results of the meta-analysis are presented in Figure 3. Five studies estimated associations with PM_{10}; however, only one study of gastric cancer,[39] one study of liver cancer,[41] and one study of pancreatic cancer[49] satisfied inclusion criteria for meta-analysis and we therefore only summarized $PM_{2.5}$ associations. RE models estimated the overall per 10-$\mu g/m^3$ increase in $PM_{2.5}$ for risk of developing the specific GI cancer subtypes of esophageal (RE = 0.92; 95% CI: 0.64, 1.20; $I^2=67.9\%$), gastric (RE = 1.01; 95% CI: 0.87, 1.15; $I^2=32.4\%$), colorectal (RE = 1.35; 95% CI: 1.08, 1.62; $I^2=88.6\%$), liver (RE = 1.31; 95% CI: 1.07, 1.56; $I^2=90.0\%$), and pancreas (RE = 1.00; 95% CI: 0.89, 1.12; $I^2=0\%$). Three studies estimated the association of $PM_{2.5}$ with all GI cancers, but only two were considered comparable for meta-analysis (RE = 1.12; 95% CI: 1.01, 1.24, $I^2=40.8\%$). Funnel plots (Figure S6) and Egger tests showed no significant asymmetry in the pattern of distribution of some GI cancer end points (esophageal, $p=0.71$; liver, $p=0.73$; GI overall, $p=0.17$), but for others the test for probability of publication bias was significant (gastric, $p<0.01$; colorectal, $p<0.01$; pancreatic, $p=0.02$) (Figure 3).

The meta-analysis results for esophageal cancer were not statistically significant, and in our hypothetical scenarios analysis the addition of one new study was less likely to change the direction of the summary estimate (Figure S1, Scenarios A and B). We found it would take the addition of five studies with findings of a higher than previously reported magnitude to alter the significance of the overall estimate (Figure S1, Scenario C). This conclusion resulted from the fact that there were only a small number of studies with equivocal findings. The estimates for stomach and pancreatic cancers were generally positive, but not always statistically significant, and, according to our *a priori*–determined criteria for testing the sensitivity of overall results, the addition of a new study could likely change or strengthen the direction of the association (Figure S2, Scenario A and Figure S3, Scenario A). With the addition of two studies of similar magnitudes to those previously reported, the overall findings could become statistically significant (Figure S2, Scenario B and Figure S3, Scenario B). We determined it is unlikely that the addition of even one study with a strong inverse association would change the direction of the summary estimate for the association between $PM_{2.5}$ and liver or colorectal cancers owing to the relatively large number of studies with consistently positive and statistically significant results (Figures S4 and S5).

Discussion

We conducted a systematic review and meta-analysis of the body of epidemiologic evidence to assess whether exposure to outdoor PM was associated with GI cancers. A relationship between increasing exposure to PM and GI cancer outcomes was observed in many studies, but this association was not always statistically significant ($p<0.05$). We concluded that there was "limited evidence of carcinogenicity" for the association between exposure to PM as a whole and diagnosis or death due to GI cancer. This classification is adapted from the IARC, where "limited" evidence refers to positive associations having been observed but

Table 4. Reported effect estimates for GI cancer outcomes and 95% CI as available from included individual human studies.

No.	Article	Study period	Participant location	Measure of association	Cancer site	Outcome	Strata	Outcome estimate[b]	95% CI
1	Ancona et al.[33,a]	2001–2010	Rome, Italy	HR per 0.027 ng/m^3 PM_{10}	Stomach	Mortality	Men	0.89	0.60, 1.34
					Stomach	Mortality	Women	0.97	0.62, 1.50
					Colon and rectum	Mortality	Men	0.82	0.58, 1.16
					Colon and rectum	Mortality	Women	0.69	0.40, 1.19
					Liver	Mortality	Men	0.66	0.29, 1.50
					Liver	Mortality	Women	1.32	0.63, 2.77
					Pancreas	Mortality	Men	1.40	1.03, 1.90
					Pancreas	Mortality	Women	1.47	1.12, 1.93
					All GI	Mortality	Men	1.09	0.85, 1.40
					All GI	Mortality	Women	1.10	0.78, 1.56
2	Bogumil et al.[49]	1993–2013	USA	HR per 10 μg/m^3 $PM_{2.5}$ and per 10 μg/m^3 PM_{10}	Pancreas	Incidence	$PM_{2.5}$	1.61	1.09, 2.37
					Pancreas	Incidence	PM_{10}	1.12	0.94, 1.32
3	Chu et al.[46]	1993–2001	USA	HR per 5.0-μg/m^3 increase in $PM_{2.5}$	Colorectal	Incidence	Overall	2.40 (1.55)[c]	1.95, 2.96 (1.40, 1.72)[c]
4	Coleman et al.[35]	1987–2014	USA	HR per 10 μg/m^3 $PM_{2.5}$	Esophagus	Mortality	Overall	0.59	0.38, 0.90
					Esophagus	Mortality	Nonsmokers	0.79	0.32, 1.96
					Stomach	Mortality	Overall	1.87	1.20, 2.92
					Stomach	Mortality	Nonsmokers	2.01	1.01, 3.98
					Colorectal	Mortality	Overall	1.29	1.05, 1.58
					Colorectal	Mortality	Nonsmokers	1.26	0.93, 1.7
					Liver	Mortality	Overall	1.32	0.94, 1.85
					Liver	Mortality	Nonsmokers	2.18	1.25, 3.81
					Pancreas	Mortality	Overall	1.09	0.83, 1.44
					Pancreas	Mortality	Nonsmokers	0.94	0.63, 1.38
5	Coleman et al.[34]	1992–2016	USA	IRR per 10 μg/m^3 $PM_{2.5}$	Esophagus	Incidence	Overall	1.08	0.88, 1.32
					Stomach	Incidence	Overall	0.96	0.79, 1.16
					Small intestine	Incidence	Overall	1.13	0.87, 1.47
					Colon	Incidence	Overall	1.05	0.96, 1.15
					Rectal	Incidence	Overall	1.15	1.01, 1.30
					Liver	Incidence	Overall	1.32	1.11, 1.57
					Pancreas	Incidence	Overall	0.98	0.85, 1.12
6	Datzmann et al.[36,a]	2010–2014	Saxony, Germany	RR per 10 μg/m^3 PM_{10}	Colorectal	Mortality	Overall	0.95	0.87, 1.04
					Colorectal	Mortality	Overall	1.78	1.71, 1.84
7	Deng et al.[37]	2000–2009	California, USA	HR per 5.0 μg/m^3 $PM_{2.5}$	Liver	Mortality	Overall	1.72 (1.31)[c]	1.62, 1.82 (1.26, 1.35)[c]
8	Ethan et al.[47,a]	2014–2016	Xi'an, China	RR per 10-μg/m^3 increase in $PM_{2.5}$	Stomach	Mortality	Overall	1.0003	1.0001, 1.002
					Colorectal	Mortality	Overall	0.9985	0.9973, 1.0004
9	Guo et al.[51]	2001–2016	Taiwan	HR per 10 μg/m^3 $PM_{2.5}$	All GI	Mortality	Overall	1.09	1.03, 1.16
					Stomach	Mortality	Overall	0.97	0.82, 1.15
					Colorectal	Mortality	Overall	1.13	1.00, 1.26
					Liver	Mortality	Overall	1.13	1.02, 1.24
10	Jerrett et al.[38,a]	1982–2000	Los Angeles, California, USA	RR per 10 μg/m^3 $PM_{2.5}$	Digestive cancer	Mortality	Overall	1.18	0.79, 1.75
11	Ma et al.[48,a]	1999–2013	Taiwan	OR per 10-μg/m^3 increase in $PM_{2.5}$	Colorectal	Incidence	Overall	1.08	1.04, 1.11
12	Nagel et al.[39]	1985–2005 (varies by region)	Sweden, Norway, Denmark, UK, Austria, Italy, Spain	HR per 5.0 μg/m^3 $PM_{2.5}$ and per 10 μg/m^3 PM_{10}	Gastric	Incidence	PM_{10}	1.07	0.79, 1.44
					Gastric	Incidence	$PM_{2.5}$	1.90 (1.38)[c]	0.98, 3.69 (0.99, 1.92)[c]
					UADT	Incidence	PM_{10}	0.93	0.64, 1.36
					UADT	Incidence	$PM_{2.5}$	1.10 (1.05)[c]	0.39, 3.13 (0.62, 1.77)[c]

Table 4. (*Continued.*)

No.	Article	Study period	Participant location	Measure of association	Cancer site	Outcome	Strata	Outcome estimate[b]	95% CI
13	Pan et al. 2015[40,a]	1991–2009	Taiwan	HR per 0.73 μg/m^3 $PM_{2.5}$	Liver	Incidence	Penghu Islets	1.22	1.02, 1.47
14	Pedersen et al.[41]	1985–2005	Denmark, Austria, Italy	HR per 5.0 μg/m^3 $PM_{2.5}$ and per 10 μg/m^3 PM_{10}	Liver	Incidence	$PM_{2.5}$	1.80 (1.34)[c]	0.58, 5.52 (0.76, 2.35)[c]
					Liver	Incidence	PM_{10}	1.44	0.83, 2.52
15	So et al.[50]	Recruited between 1985 to 2005 and followed until 2011 to 2015	Sweden, Denmark, Netherlands, France, Austria	HR per 5.0 μg/m^3 $PM_{2.5}$	Liver	Incidence	$PM_{2.5}$	1.25 (1.12)[c]	0.85, 185 (0.92, 1.36)[c]
16	Turner et al.[42]	1982–2004	USA	HR per 4.4 μg/m^3 $PM_{2.5}$	Esophagus	Mortality	Overall	1.05 (1.02)[c]	0.83, 1.32 (0.93, 1.13)[c]
					Stomach	Mortality	Overall	1.00 (1.00)[c]	0.82, 1.22 (0.93, 1.13)[c]
					Colorectal	Mortality	Overall	1.09 (1.04)[c]	1.00, 1.19 (1.00, 1.08)[c]
					Liver	Mortality	Overall	1.12 (1.05)[c]	0.89, 1.40 (0.94, 1.16)[c]
					Pancreas	Mortality	Overall	0.96 (0.98)[c]	0.85, 1.07 (0.92, 1.03)[c]
17	VoPham et al.[43]	2000–2014	USA	IRR per 10 μg/m^3 $PM_{2.5}$	Liver	Incidence	Overall	1.26	1.08, 1.47
18	Wang et al.[44,a]	1999–2009	China	RR per 10 μg/m^3 $PM_{2.5}$	Pancreas	Mortality	Overall	1.16	1.13, 1.20
19	Weinmayr et al.[45,a]	1985–2005	Norway, Sweden, Denmark, Netherlands, Austria, Italy	HR per 5 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ Cu	1.05	0.72, 1.53
					UADT	Incidence	$PM_{2.5}$Cu	1.02	0.78, 1.33
				HR per 100 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ Fe	1.03	0.75, 1.42
					UADT	Incidence	$PM_{2.5}$ Fe	0.90	0.73, 1.1
				HR per 50 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ K	1.21	0.88, 1.66
					UADT	Incidence	$PM_{2.5}$ K	1.12	0.83, 1.51
				HR per 1 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ Ni	0.81	0.36, 1.83
					UADT	Incidence	$PM_{2.5}$ Ni	0.84	0.51, 1.37
				HR per 200 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ S	1.93	1.13, 3.27
					UADT	Incidence	$PM_{2.5}$S	0.75	0.25, 2.21
				HR per 100 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ Si	0.90	0.41, 1.98
					UADT	Incidence	$PM_{2.5}$ Si	0.76	0.54, 1.05
				HR per 2 ng/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ V	0.90	0.45, 1.81
					UADT	Incidence	$PM_{2.5}$ V	0.68	0.41, 1.12
				HR per 10 μg/m^3 $PM_{2.5}$	Gastric	Incidence	$PM_{2.5}$ Zn	1.63	0.88, 3.01
					UADT	Incidence	$PM_{2.5}$ Zn	1.11	0.82, 1.51
20	Wong et al.[13]	1998–2001	Hong Kong	IRR per 10 μg/m^3 $PM_{2.5}$	GI	Mortality	Overall	1.22	1.05, 1.42
					Upper GI tract	Mortality	Overall	1.42	1.06, 1.89
					Lower GI	Mortality	Overall	1.01	0.79, 1.30
					GI accessory	Mortality	Overall	1.35	1.06, 1.71

Note: CI, confidence interval; Cu, copper; Fe, iron; GI, gastrointestinal; HR, hazard ratio; IRR, incidence rate ratio; K, potassium; Ni, nickel; OR, odds ratio; $PM_{2.5}$, PM ≤2.5 μm in aerodynamic diameter; PM_{10}, PM ≤10 μm in aerodynamic diameter; RR, risk ratio; S, sulfur; Si, silicon; UADT, upper aero digestive tract; V, vanadium; Zn, Zinc.

[a]Excluded from meta-analysis due to high risk of bias or heterogeneity in study design, which limited comparability with other studies.

[b]Fully adjusted outcome estimates reported as available from included individual articles.

[c]Standardized to a 10-μg/m^3 increase in $PM_{2.5}$ (original values included in parenthesis).

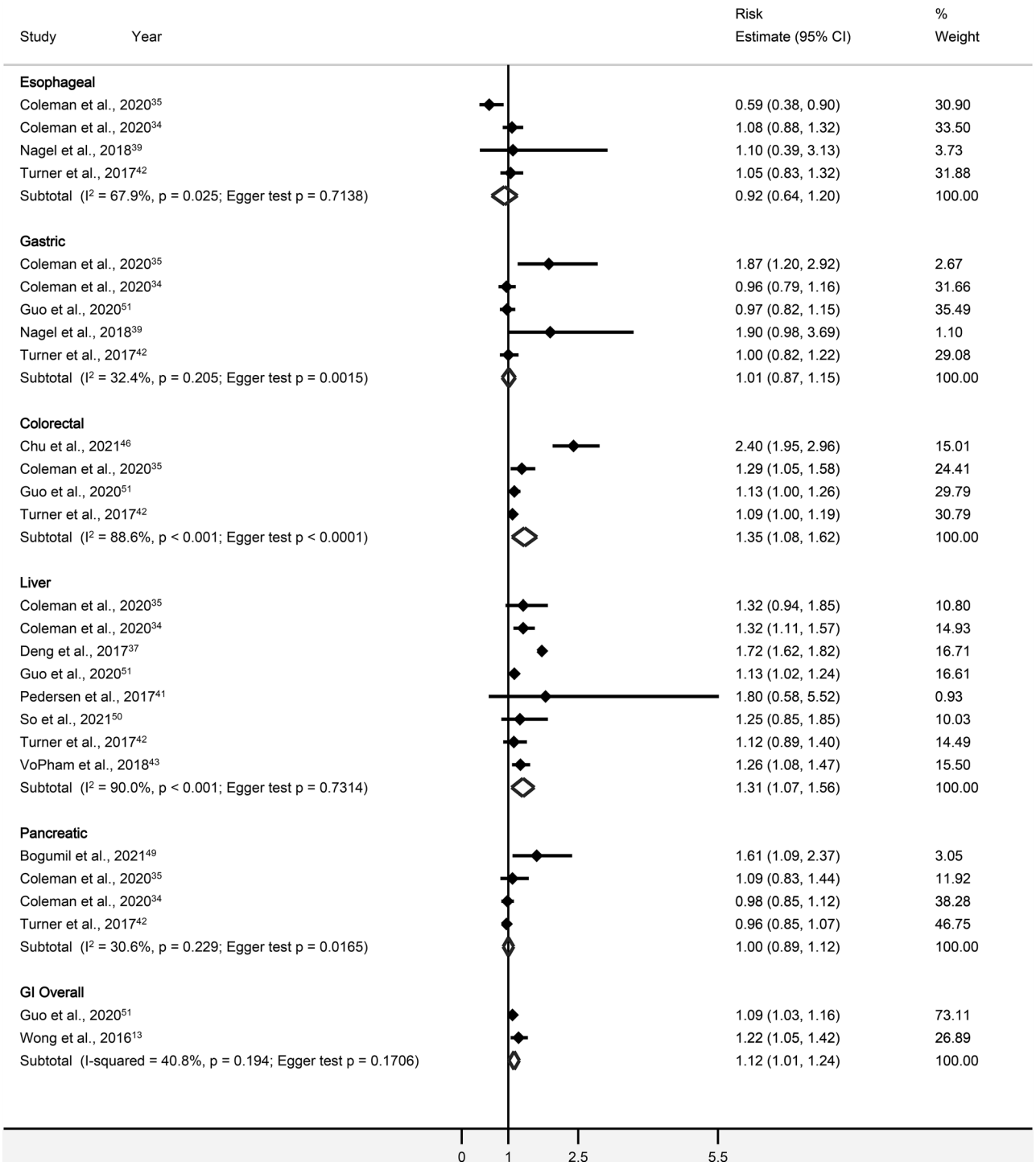

Figure 3. Meta-analysis of included epidemiologic studies. Reported effect estimates (95% CI) from individual studies (inverse-variance weighted, represented by size of rectangle) and overall pooled estimate from random-effects (RE) model for PM exposure and GI cancer subtypes *a*) esophageal, *b*) gastric, *c*) colorectal, *d*) liver, *e*) pancreas, and *f*) overall. Note: CI, confidence interval; GI, gastrointestinal; PM, particulate matter.

that bias and confounding cannot be ruled out with reasonable confidence.[30] Although the current literature is of moderate quality, inconsistent, and small, the results from our meta-analysis indicate that PM exposure may be associated with mortality or incidence for some GI cancers, such as colorectal and liver. The most frequently evaluated relationship was the association between $PM_{2.5}$ exposure and both incidence and mortality from liver cancers; this was also the site for which the evidence was strongest. This review also highlights opportunities for future research because we found that the inclusion of additional, high-quality studies could change these conclusions.

One motivation for our review was the recognition that biologic plausibility exists for a relationship between outdoor air pollution exposures and the development of GI cancers. There are several hypothesized mechanisms for this potential association. For instance, alterations in the function of the gut microbiota

may contribute to chronic GI disease, an important risk factor for GI cancers.[13,57,58,59] Small particles readily absorbed in the lungs following inhalation can be delivered through the bloodstream and deposited in other body tissues, including the gut.[60] PM that reaches the bronchioles and alveolar spaces may also be phagocytosed by alveolar macrophages,[61] where, once sequestered, it is trapped in the airway by a protective mucus layer.[62] In healthy individuals, the trapped particles are propelled by cilia through the oropharynx and into the GI tract through a process called mucociliary clearance.[15] As a result, a portion of the internal exposure to PM occurs in the upper GI tract. Mucociliary transport of PM inhaled in the lungs and then cleared into the upper GI tract has been demonstrated in human studies of nonsmokers.[16] Upper GI cancers are also etiologically distinct and PM could theoretically act differentially on their development or progression; to our knowledge, animal and mechanistic data are lacking to evaluate this hypothesis.

Our review identified important research gaps that should inform future work on this topic. Because of the highly fatality of some GI cancers, diagnosis and death typically occur within $\leq$5 y.[2] For cancers with better prognosis, mortality assessments may be a better indicator of survival than susceptibility to development of new disease. Few articles identified by this review had information on cancer subtype, and several presented results for GI cancer overall or by upper and lower GI tract. Further, the etiology of cancers of the GI tract varies from organ to organ; future investigations need to consider the potential varying biological mechanisms at play by developing hypotheses for specific cancer end points. Analyses that combine cancer subtypes with differing etiologies may cause underestimation of the magnitude of the relationship if PM is truly associated with risk of only certain subtypes. Future studies should strive to evaluate associations with GI cancers and PM by subtype with a sufficient number of cases for each analysis. As the number of different cancer end points assessed in one study increases, so does concern for chance findings of statistical significance (either positive or inverse).[63]

We identified widely varying approaches to exposure assessment across this small number of studies that leads us to several related recommendations. Ideally, PM exposure assessments should characterize the time window most relevant for GI cancer development. Most of the studies we evaluated in our review were limited by exposure assessment occurring at or near the time of study enrollment, which may not be sufficient to account for the long latency of most GI cancers.[64] This may be one explanation for a lack of observed association in some studies. Fine-scale $PM_{2.5}$ measurements are generally not available prior to when they were routinely collected following their regulation in the late 1990s in the United States[65] and in the 2000s in Europe,[66] so most studies would be unable to retrospectively assess exposure. Although several studies in the United States relied on back extrapolation and other interpolation techniques to fill in missing exposure information,[34,35,49] no study in our review evaluated exposures during the period prior to study start, which may be the most etiologically relevant. Moreover, the averaging period for exposure was highly varied across studies and included single-year averages or modeled estimates intended to reflect exposure over longer time periods.[33,38,39,43,50] The United States Multi-Ethnic Cohort Study was the only study to implement a time-varying analysis approach, based on monthly averages.[51] The small number of studies coupled with varying time windows of exposure limits meaningful interpretation about whether the hypothesized relationship between $PM_{2.5}$ and GI cancers is driven by acute or chronic exposure. Future work incorporating advanced statistical approaches to differentiate the role of exposures during different periods of life[67] could reveal whether there are critical windows of exposure. The assessment of air pollution exposure using only community average concentrations, which was the case for about a third of the studies we reviewed, may not represent the individual-level association between PM and GI cancers. Area-level estimates of PM do not account for the spatial variability in exposures at residential addresses and this misclassification of exposure would likely have attenuated associations toward the null. About half of the studies included multipollutant models, providing confidence in associations with PM that remained even after controlling for levels of other outdoor air pollutants. The linear increases in PM used in most studies to calculate the measure of association allows comparison between studies and enables contribution to regulatory reviews.

Almost all studies included in our review described the inability to assess PM exposure anywhere other than the baseline residence location as a study limitation. Although some analyses adjusted for information about occupation, none included exposure assessed at a work address, and variation in exposure between residence and place of work may have led to exposure misclassification. The expectation is that such misclassification would be nondifferential, therefore, leading to attenuation of any association between PM and GI cancer risk or mortality. Future studies could mitigate this concern by adding assessments of PM exposure from other microenvironments, such as at work or during the commute. In addition, individuals who change addresses will have different exposures at each residence. For this reason, studies should optimally assess exposures at all residence locations during relevant exposure periods or conduct sensitivity analyses with movers excluded. Because outdoor air pollution is so varied regionally in both total burden and its constituency, the lack of geographic heterogeneity in the existing studies, which were largely from the United States, Europe, and China, was a limitation of our meta-analyses. Our synthesis did not include studies in Africa, where the reasons for high rates of esophageal cancer are still being explored.[21] Additional studies from both the northern and southern hemispheres would contribute meaningful data to a body of literature that currently is lacking in evaluations of populations within these areas.

The inability of some of the included analyses to control for key variables—such as SES, smoking, physical activity, and copollutant exposures—could have led to residual confounding in these evaluations and subsequently biased the interpretations in this review. Controlling for some of these factors is important because they are potentially correlated with PM exposure,[68,69] and evaluation of these factors as potential confounders should be a goal for future research efforts. Other factors could contribute to differences in baseline risk owing to differences in underlying biology (e.g., sex) or in susceptibility (e.g., cigarette smoking).[70,71] Few articles had the power to evaluate effect modification, but interactions are biologically plausible, and their study is warranted.

Confidence in the summary relationship from our evaluation is constrained by the moderate quality and inconsistency of findings across individual studies as well as the small number of evaluations by specific GI cancer type. Most studies we reviewed identified at least one statistically significant positive association between PM exposure and risk of at least one GI cancer end point of incidence or mortality. Only three reported no statistically significant relationships,[38,39,41] but there remain only a small numbers of studies that have investigated these associations to date and the number for each specific cancer are few. For instance, only four of our included articles evaluated the association with esophageal cancer.[34,35,39,42] As such, we acknowledge the potential for chance findings in our meta-analysis. The nascent state of the literature could also suggest the possibility of publication bias

across studies, which we formally evaluated and found some evidence of. We determined it unlikely that the addition of a new study would change the results of the meta-analysis for liver or colorectal cancers, for which the number of studies were larger and study results were consistently positive and statistically significant. However, the meta-analysis results for the other GI cancer subtypes were less definitive. Taken together, our findings underscore the need for additional studies of specific gastric cancer sites given that the addition of new studies could alter current conclusions or provide further confidence about associations with PM exposure.

This work contributes a novel synthesis of a small number of epidemiologic studies of the association between outdoor PM and GI cancers, an interesting and biologically plausible—but still understudied—relationship. A particular strength of this work was our assessment of the likelihood of bias in each analysis. We note general interpretations of the expected direction of impacts of these various criteria above, including combining cancer subtypes, multiple comparisons, control for confounding, and nonspecific/ecologic exposure estimates. Although the exact direction of bias is hard to predict in every circumstance, we would expect most to be nondifferential, which would lead to underestimation of the true magnitudes of associations. However, future reviews inclusive of a greater number of studies might find evaluation of the anticipated direction of the bias on the effect estimate for each individual study to contribute meaningfully to interpretations. We combined incidence and mortality studies in our evaluation, given the small number of studies for any one cancer site and because patterns of incidence and mortality are similar for most of these cancers.[72,73,74,75] We note some exceptions, however, in that patterns of incidence and mortality for colorectal cancer can be quite divergent[76] and our meta-analysis of this site included only mortality studies. There were also more studies of incident liver cancer than liver cancer death, and this was the most commonly studied upper GI cancer among the studies we evaluated. The small number of studies overall did not allow us to further explore potential differential relationships of PM on incidence versus mortality for these cancers.

Conclusions

We conducted a systematic review and meta-analysis of the epidemiologic evidence of exposure to PM air pollution and GI cancer and concluded that although positive associations were consistently reported, evidence of associations is limited based on the moderate quality and inconsistency in findings across a small number of studies. Future researchers should strive to conduct more studies in the most affected geographic areas for GI cancers, evaluate the impact of different PM exposure assessment approaches on observed associations, and include investigation of cancer subtypes and specific chemical components of PM.

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References

1. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. 2020. Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 159(1):335–349.e15, PMID: 32247694, https://doi.org/10.1053/j.gastro.2020.02.068.
2. Arnold M, Rutherford MJ, Bardot A, Ferlay J, Andersson TML, Myklebust TÅ, et al. 2019. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol. 20(11):1493–1505, PMID: 31521509, https://doi.org/10.1016/S1470-2045(19)30456-5.
3. U.S. EPA (U.S. Environmental Protection Agency). 2017. What is particulate matter? https://www3.epa.gov/region1/eco/uep/particulatematter.html [accessed 25 January 2022].
4. U.S. EPA, 2021. Particulate Matter (PM) Pollution. https://www.epa.gov/pm-pollution [accessed 1 December 2021].
5. WHO (World Health Organization) Regional Office for Europe. 2013. *Health Effects of Particulate Matter. Policy Implications for Countries in Eastern Europe, Caucasus and Central Asia*. Copenhagen, Denmark: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/344854/9789289000017-eng.pdf?sequence=1&isAllowed=y [accessed 25 January 2022].
6. Kim KH, Kabir E, Kabir S. 2015. A review on the human health impact of airborne particulate matter. Environ Int 74:136–143, PMID: 25454230, https://doi.org/10.1016/j.envint.2014.10.005.
7. U.S. EPA. 2019. Outdoor Air Quality. https://www.epa.gov/report-environment/outdoor-air-quality [accessed 1 December 2021].
8. WHO. 2021. Household air pollution and health. https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health [accessed 1 December 2021].
9. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2016. Outdoor Air Pollution. IARC Monogr Eval Carcinog Risk Hum 109:9–444, PMID: 29905447.
10. Turner MC, Andersen ZJ, Baccarelli A, Diver WR, Gapstur SM, Pope CA III, et al. 2020. Outdoor air pollution and cancer: an overview of the current evidence and public health recommendations. CA Cancer J Clin 70(6):460–479, PMID: 32964460, https://doi.org/10.3322/caac.21632.
11. Gabet S, Lemarchand C, Guénel P, Slama R. 2021. Breast cancer risk in association with atmospheric pollution exposure: a meta-analysis of effect estimates followed by a health impact assessment. Environ Health Perspect 129(5):57012, PMID: 34038220, https://doi.org/10.1289/EHP8419.
12. Ghio AJ, Kim C, Devlin RB. 2000. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. Am J Respir Crit Care Med 162(3 pt 1):981–988, PMID: 10988117, https://doi.org/10.1164/ajrccm.162.3.9911115.
13. Wong CM, Tsang H, Lai HK, Thomas GN, Lam KB, Chan KP, et al. 2016. Cancer mortality risks from long-term exposure to ambient fine particle. Cancer Epidemiol Biomarkers Prev 25(5):839–845, PMID: 27197138, https://doi.org/10.1158/1055-9965.EPI-15-0626.
14. Alfaro-Moreno E, Martínez L, García-Cuellar C, Bonner JC, Murray JC, Rosas I, et al. 2002. Biologic effects induced *in vitro* by PM_{10} from three different zones of Mexico City. Environ Health Perspect 110(7):715–720, PMID: 12117649, https://doi.org/10.1289/ehp.02110715.
15. Munkholm M, Mortensen J. 2014. Mucociliary clearance: pathophysiological aspects. Clin Physiol Funct Imaging 34(3):171–177, PMID: 24119105, https://doi.org/10.1111/cpf.12085.
16. Möller W, Häussinger K, Winkler-Heil R, Stahlhofen W, Meyer T, Hofmann W, et al. 2004. Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. J Appl Physiol (1985) 97(6):2200–2206, PMID: 15347631, https://doi.org/10.1152/japplphysiol.00970.2003.
17. Kim HB, Shim JY, Park B, Lee YJ. 2018. Long-term exposure to air pollutants and cancer mortality: a meta-analysis of cohort studies. Int J Environ Res Public Health 15(15):2608, PMID: 30469439, https://doi.org/10.3390/ijerph15112608.
18. Kayamba V, Heimburger DC, Morgan DR, Atadzhanov M, Kelly P. 2017. Exposure to biomass smoke as a risk factor for oesophageal and gastric cancer in low-income populations: a systematic review. Malawi Med J 29(2):212–217, PMID: 28955435, https://doi.org/10.4314/mmj.v29i2.25.
19. Josyula S, Lin J, Xue X, Rothman N, Lan Q, Rohan TE, et al. 2015. Household air pollution and cancers other than lung: a meta-analysis. Environ Health 14:24, PMID: 25890249, https://doi.org/10.1186/s12940-015-0001-3.
20. Okello S, Akello SJ, Dwomoh E, Byaruhanga E, Opio CK, Zhang R, et al. 2019. Biomass fuel as a risk factor for esophageal squamous cell carcinoma: a systematic review and meta-analysis. Environ Health 18(1):60, PMID: 31262333, https://doi.org/10.1186/s12940-019-0496-0.
21. Van Loon K, Mwachiro MM, Abnet CC, Akoko L, Assefa M, Burgert SL, et al. 2018. The African Esophageal Cancer Consortium: a call to action. J Glob Oncol 4:1–9, PMID: 30241229, https://doi.org/10.1200/JGO.17.00163.
22. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4(1):1, PMID: 25554246, https://doi.org/10.1186/2046-4053-4-1.
23. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 350:g7647, PMID: 25555855, https://doi.org/10.1136/bmj.g7647.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 134:178–189, PMID: 33789819, https://doi.org/10.1016/j.jclinepi.2021.03.001.

25. Woodruff TJ, Sutton P. 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect 122(10):1007–1014, PMID: 24968373, https://doi.org/10.1289/ehp.1307175.
26. Covidence. 2022. Terms of Service. https://www.covidence.org/terms/ [accessed 25 January 2022].
27. Higgins JPT, Green S. 2011. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0.* New York, NY: John Wiley & Sons. https://handbook-5-1.cochrane.org/ [accessed 25 January 2022].
28. Viswanathan M, Ansari M, Berkman N, Chang S, Hartling L, McPheeters M, et al. 2008. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In: *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/products/methods-guidance-bias-individual-studies/methods [accessed 25 January 2022].
29. U.S. EPA. 2019. *Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019).* EPA/600/R-19/188. Washington, DC: U.S. Environmental Protection Agency.
30. IARC (International Agency for Research on Cancer). 2019. *Preamble to the International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans*. Amended January 2019. Lyon, France: IARC. https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf [accessed 25 January 2022].
31. DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188, PMID: 3802833, https://doi.org/10.1016/0197-2456(86)90046-2.
32. Egger M, Davey Smith G, Schneider M, Minder C. 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634, PMID: 9310563, https://doi.org/10.1136/bmj.315.7109.629.
33. Ancona C, Badaloni C, Mataloni F, Bolignano A, Bucci S, Cesaroni G, et al. 2015. Mortality and morbidity in a population exposed to multiple sources of air pollution: a retrospective cohort study using air dispersion models. Environ Res 137:467–474, PMID: 25701728, https://doi.org/10.1016/j.envres.2014.10.036.
34. Coleman NC, Burnett RT, Ezzati M, Marshall JD, Robinson AL, Pope CA III. 2020. Fine particulate matter exposure and cancer incidence: analysis of SEER cancer registry data from 1992–2016. Environ Health Perspect 128(10):107004, PMID: 33035119, https://doi.org/10.1289/EHP7246.
35. Coleman NC, Burnett RT, Higbee JD, Lefler JS, Merrill RM, Ezzati M, et al. 2020. Cancer mortality risk, fine particulate air pollution, and smoking in a large, representative cohort of US adults. Cancer Causes Control 31(8):767–776, PMID: 32462559, https://doi.org/10.1007/s10552-020-01317-w.
36. Datzmann T, Markevych I, Trautmann F, Heinrich J, Schmitt J, Tesch F. 2018. Outdoor air pollution, green space, and cancer incidence in Saxony: a semi-individual cohort study. BMC Public Health 18(1):715, PMID: 29884153, https://doi.org/10.1186/s12889-018-5615-2.
37. Deng H, Eckel SP, Liu L, Lurmann FW, Cockburn MG, Gilliland FD. 2017. Particulate matter air pollution and liver cancer survival. Int J Cancer 141(4):744–749, PMID: 28589567, https://doi.org/10.1002/ijc.30779.
38. Jerrett M, Burnett RT, Ma R, Pope CA III, Krewski D, Newbold KB, et al. 2005. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 16(6):727–736, PMID: 16222161, https://doi.org/10.1097/01.ede.0000181630.15826.7d.
39. Nagel G, Stafoggia M, Pedersen M, Andersen ZJ, Galassi C, Munkenast J, et al. 2018. Air pollution and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts for Air Pollution Effects (ESCAPE). Int J Cancer 143(7):1632–1643, PMID: 29696642, https://doi.org/10.1002/ijc.31564.
40. Pan WC, Wu CD, Chen MJ, Huang YT, Chen CJ, Su HJ, et al. 2015. Fine particle pollution, alanine transaminase, and liver cancer: a Taiwanese prospective cohort study (REVEAL-HBV). J Natl Cancer Inst 108(3):djv341, PMID: 26561636, https://doi.org/10.1093/jnci/djv341.
41. Pedersen M, Andersen ZJ, Stafoggia M, Weinmayr G, Galassi C, Sørensen M, et al. 2017. Ambient air pollution and primary liver cancer incidence in four European cohorts within the ESCAPE project. Environ Res 154:226–233, PMID: 28107740, https://doi.org/10.1016/j.envres.2017.01.006.
42. Turner MC, Krewski D, Diver WR, Pope CA III, Burnett RT, Jerrett M, et al. 2017. Ambient air pollution and cancer mortality in the Cancer Prevention Study II. Environ Health Perspect 125(8):087013, PMID: 28886601, https://doi.org/10.1289/EHP1249.
43. VoPham T, Bertrand KA, Tamimi RM, Laden F, Hart JE. 2018. Ambient $PM_{2.5}$ air pollution exposure and hepatocellular carcinoma incidence in the United States. Cancer Causes Control 29(6):563–572, PMID: 29696510, https://doi.org/10.1007/s10552-018-1036-x.
44. Wang Y, Li M, Wan X, Sun Y, Cheng K, Zhao X, et al. 2018. Spatiotemporal analysis of $PM_{2.5}$ and pancreatic cancer mortality in China. Environ Res 164:132–139, PMID: 29486344, https://doi.org/10.1016/j.envres.2018.02.026.
45. Weinmayr G, Pedersen M, Stafoggia M, Andersen ZJ, Galassi C, Munkenast J, et al. 2018. Particulate matter air pollution components and incidence of cancers of the stomach and the upper aerodigestive tract in the European Study of Cohorts of Air Pollution Effects (ESCAPE). Environ Int 120:163–171, PMID: 30096610, https://doi.org/10.1016/j.envint.2018.07.030.
46. Chu H, Xin J, Yuan Q, Wu Y, Du M, Zheng R, et al. 2021. A prospective study of the associations among fine particulate matter, genetic variants, and the risk of colorectal cancer. Environ Int 147:106309, PMID: 33338681, https://doi.org/10.1016/j.envint.2020.106309.
47. Ethan CJ, Mokoena KK, Yu Y, Shale K, Fan Y, Rong J, et al. 2020. Association between $PM_{2.5}$ and mortality of stomach and colorectal cancer in Xi'an: a time-series study. Environ Sci Pollut Res Int 27(18):22353–22363, PMID: 32314282, https://doi.org/10.1007/s11356-020-08628-0.
48. Ma JW, Lai TJ, Hu SY, Lin TC, Ho WC, Tsan YT. 2020. Effect of ambient air pollution on the incidence of colorectal cancer among a diabetic population: a nationwide nested case–control study in Taiwan. BMJ Open 10(10):e036955, PMID: 33115890, https://doi.org/10.1136/bmjopen-2020-036955.
49. Bogumil D, Wu AH, Stram D, Yang J, Tseng CC, Le Marchand L, et al. 2021. The association between ambient air pollutants and pancreatic cancer in the Multiethnic Cohort Study. Environ Res 202:111608, PMID: 34214566, https://doi.org/10.1016/j.envres.2021.111608.
50. So R, Chen J, Mehta AJ, Liu S, Strak M, Wolf K, et al. 2021. Long-term exposure to air pollution and liver cancer incidence in six European cohorts. Int J Cancer 149(11):1887–1897, PMID: 34278567, https://doi.org/10.1002/ijc.33743.
51. Guo C, Chan TC, Teng YC, Lin C, Bo Y, Chang LY, et al. 2020. Long-term exposure to ambient fine particles and gastrointestinal cancer mortality in Taiwan: a cohort study. Environ Int 138:105640, PMID: 32179321, https://doi.org/10.1016/j.envint.2020.105640.
52. Liao D, Peuquet DJ, Duan Y, Whitsel EA, Dou J, Smith RL, et al. 2006. GIS approaches for the estimation of residential-level ambient PM concentrations. Environ Health Perspect 114(9):1374–1380, PMID: 16966091, https://doi.org/10.1289/ehp.9169.
53. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and PM_{coarse} in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46(20):11195–11205, PMID: 22963366, https://doi.org/10.1021/es301948k.
54. Li L, Losser T, Yorke C, Piltner R. 2014. Fast inverse distance weighting-based spatiotemporal interpolation: a web-based application of interpolating daily fine particulate matter $PM_{2.5}$ in the contiguous U.S. using parallel programming and k-d tree. Int J Environ Res Public Health 11(9):9101–9141, PMID: 25192146, https://doi.org/10.3390/ijerph110909101.
55. Kim SY, Bechle M, Hankey S, Sheppard L, Szpiro AA, Marshall JD. 2020. Concentrations of criteria pollutants in the contiguous U.S., 1979–2015: role of prediction model parsimony in integrated empirical geographic regression. PLoS One 15(2):e0228535, PMID: 32069301, https://doi.org/10.1371/journal.pone.0228535.
56. Beckerman BS, Jerrett M, Serre M, Martin RV, Lee SJ, van Donkelaar A, et al. 2013. A hybrid approach to estimating national scale spatiotemporal variability of $PM_{2.5}$ in the contiguous United States. Environ Sci Technol 47(13):7233–7241, PMID: 23701364, https://doi.org/10.1021/es400039u.
57. Risom L, Møller P, Loft S. 2005. Oxidative stress-induced DNA damage by particulate air pollution. Mutat Res 592(1–2):119–137, PMID: 16085126, https://doi.org/10.1016/j.mrfmmm.2005.06.012.
58. Mantovani A, Allavena P, Sica A, Balkwill F. 2008. Cancer-related inflammation. Nature 454(7203):436–444, PMID: 18650914, https://doi.org/10.1038/nature07205.
59. Lewtas J. 2007. Air pollution combustion emissions: characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects. Mutat Res 636(1–3):95–133, PMID: 17951105, https://doi.org/10.1016/j.mrrev.2007.08.003.
60. Beamish LA, Osornio-Vargas AR, Wine E. 2011. Air pollution: an environmental factor contributing to intestinal disease. J Crohns Colitis 5(4):279–286, PMID: 21683297, https://doi.org/10.1016/j.crohns.2011.02.017.
61. Mutlu EA, Comba IY, Cho T, Engen PA, Yazıcı C, Soberanes S, et al. 2018. Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. Environ Pollut 240:817–830, PMID: 29783199, https://doi.org/10.1016/j.envpol.2018.04.130.
62. Bustamante-Marin XM, Ostrowski LE. 2017. Cilia and mucociliary clearance. Cold Spring Harb Perspect Biol 9(4):a028241, PMID: 27864314, https://doi.org/10.1101/cshperspect.a028241.
63. Ranganathan P, Pramesh CS, Buyse M. 2016. Common pitfalls in statistical analysis: the perils of multiple testing. Perspect Clin Res 7(2):106–107, PMID: 27141478, https://doi.org/10.4103/2229-3485.179436.
64. Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D. 2017. *Cancer Epidemiology and Prevention*. 4th ed. Thun M, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D, eds. New York, NY: Oxford University Press
65. U.S. EPA. 1990. Clean Air Act Amendment Summary: Title I. https://www.epa.gov/clean-air-act-overview/1990-clean-air-act-amendment-summary-title-i [accessed 1 December 2021].
66. Priemus H, Schutte-Postma E. 2009. Notes on the particulate matter standards in the European Union and the Netherlands. Int J Environ Res Public Health 6(3):1155–1173, PMID: 19440439, https://doi.org/10.3390/ijerph6031155.

67. Gasparrini A. 2014. Modeling exposure–lag–response associations with distributed lag non-linear models. Stat Med 33(5):881–899, PMID: 24027094, https://doi.org/10.1002/sim.5963.
68. Roberts JD, Voss JD, Knight B. 2014. The association of ambient air pollution and physical inactivity in the United States. PLoS One 9(3):e90143, PMID: 24598907, https://doi.org/10.1371/journal.pone.0090143.
69. Zou B, Peng F, Wan N, Mamady K, Wilson GJ. 2014. Spatial cluster detection of air pollution exposure inequities across the United States. PLoS One 9(3): e91917, PMID: 24647354, https://doi.org/10.1371/journal.pone.0091917.
70. O'Neill MS, Breton CV, Devlin RB, Utell MJ. 2012. Air pollution and health: emerging information on susceptible populations. Air Qual Atmos Health 5(2):189–201, PMID: 25741389, https://doi.org/10.1007/s11869-011-0150-7.
71. Annesi-Maesano I, Agabiti N, Pistelli R, Couilliot MF, Forastiere F. 2003. Subpopulations at increased risk of adverse health outcomes from air pollution. Eur Respir J 21(suppl 40):57s–63s, PMID: 12762576, https://doi.org/10.1183/09031936.03.00402103.
72. Wong MCS, Hamilton W, Whiteman DC, Jiang JY, Qiao Y, Fung FDH, et al. 2018. Global incidence and mortality of oesophageal cancer and their correlation with socioeconomic indicators temporal patterns and trends in 41 countries. Sci Rep 8(1):4522, PMID: 29540708, https://doi.org/10.1038/s41598-018-19819-8.
73. Rawla P, Barsouk A. 2019. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol 14(1):26–38, PMID: 30944675, https://doi.org/10.5114/pg.2018.80001.
74. Wong MCS, Jiang JY, Goggins WB, Liang M, Fang Y, Fung FDH, et al. 2017. International incidence and mortality trends of liver cancer: a global profile. Sci Rep 7:45846, PMID: 28361988, https://doi.org/10.1038/srep45846.
75. Rawla P, Sunkara T, Gaduputi V. 2019. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol 10(1):10–27, PMID: 30834048, https://doi.org/10.14740/wjon1166.
76. Rawla P, Sunkara T, Barsouk A. 2019. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol 14(2):89–103, PMID: 31616522, https://doi.org/10.5114/pg.2018.81072.